Longitudinal Exposure to Non-Persistent Insecticides and Cognitive and Physical Neural Function of Children

Specific Aim: To examine the relationship between aggregate and cumulative exposure to non-persistent insecticides and neurological development of children.

Hypothesis: After adjusting for potential confounders, exposure to non-persistent insecticides such as carbamates, organophosphates, and pyrethroids, is negatively associated with performance on neurobehavioral (e.g., IQ) and neuromuscular (e.g., postural balance) measures.

Sub-Hypotheses:

a) Body burdens or excretion rates of non-persistent insecticides or their metabolites in children are directly related to insecticide concentrations in environmental exposure media and human behaviors.

b) Longitudinal insecticide exposure for individual children can be ascertained from repeated (e.g., quarterly) short-term sampling of non-invasive biological markers of exposure (e.g., insecticide metabolites in urine).

c) Longitudinal insecticide exposure for individual children can be estimated from repeated (e.g., annual) residential exposure media (e.g., settled dust indoors) and longitudinal questionnaire/diary information on residential pest pressure, residential insecticide use, microactivity patterns, and food consumption.

d) Long-term (e.g., annual) exposure to non-persistent insecticides varies among groups of children defined by age and other demographic parameters.

e) Long-term exposure to non-persistent insecticides for populations of children can be estimated from personal exposure information obtained from representative samples of individual children.

Public Health Significance

Members of the pyrethroid and organophosphate classes of synthetic insecticides have been identified as toxic to developing nervous systems (Olson et al. 1998; Roy et al. 1998; Weiss 2000). Data from animal models and epidemiological studies suggest that even low levels of exposure during critical periods of development could cause subtle neurological effects in humans (Dam

et al. 1999; Miller 1999; Auman et al. 2000; Dam et al. 2000; Rice and Barone 2000; Ritz and Yu 2000). For example, permethrin, a commonly used pyrethroid insecticide in the United States (Landrigan et al. 1999), adversely impacts synaptogenesis in the developing nervous system (Rice and Barone 2000). The human central nervous system develops from the first few weeks of gestation through puberty with synaptogenesis occurring most rapidly during gestation through 4 to 5 years of age (Rice and Barone 2000).

Clinical outcomes resulting from cumulative insecticide exposure are unknown. However, diagnoses of several outcomes such as autism and ADD have been on the rise. This study will investigate relationships between such outcomes and levels of insecticide exposures. The relationship between insecticide exposures and decreases in IQ, effects that impact an individual's quality of life, will also be investigated.

A 1999 report issued by the Centers for Disease Control and Prevention (CDC) indicated that more than 90% of a sample of the U.S. population (The National Health and Nutrition Examination Survey, NHANES) had detectible levels of at least 3 metabolites of organophosphate insecticides in their blood or urine. The metabolites detected in the highest proportion of the sample, diethylphosphate(DEP), diethylthiophosphate(DETP), are non-specific metabolites of approximately 10 regularly used organophosphate insecticides.

In addition, a report by the General Accounting Office indicates that Federal, state, and local public health agencies are in better need for estimates of reference values for human exposure to chemicals and the variability in these values (GAO, 2000). This research will generate high quality data on exposures of the U.S. Population to insecticides and the geographic and temporal variability in those exposures.

Justification for Large Prospective Study

The time windows of greatest vulnerability to disruption of neural development vary by substance, dose of the substance, and mechanism of action (Adams et al. 2000). Thus, an in-depth understanding of numerous variables, including short-, intermediate-, and long-term intake of insecticides is needed to investigate potential exposure-disease relationships. A prospective longitudinal cohort study is the most powerful design for investigating relationships of this type.

Pesticide exposures in children are highly variable, not only among different children but also for the same child measured at different time points (Quackenboss *et al.*, 2000; Rigas *et al.*, 2001). As a result, many measurements are needed to accurately characterize acute, longitudinal, and long-term exposure for individuals. Using a repeated measures design will increase the accuracy and precision of the estimates and will increase the likelihood of observing a relationship between the exposures and neurodevelopmental health outcomes, if one exists. Repeated measures obtained from a large cohort will also allow us to gain a better understanding of variability in the exposure-effect relationship and the associated explanatory factors.

The types and quantities of pesticides used are highly variable by region of the country. Since cumulative exposure to several pesticides is of interest, any analysis will be multi-variate. Individuals diagnosed with the health effects of interest, however, will be relatively few in number. Because of the relatively rare outcomes and because of the large gradients in exposure, a large sample size is warranted. Scientific contributions to this proposal from the Study Design Working Group and other parties will enhance the significance this aspect of the proposed hypothesis.

A large sample size will allow those components of this hypothesis that are related to validation of exposure estimation methods (e.g. GIS, surveys, etc) to be tested on a smaller sub-sample of the study population. An additional benefit of a large sample size is that it will provide meaningful data to and encourage support from state and regional health departments, who might otherwise have little interest.

Scientific Merit

The scientific outcomes of this hypothesis will be two-fold: 1) examination of the relationship between longitudinal exposure to non-persistent insecticides and incidence of neurological outcomes in children; 2) ascertainment of valid and reliable biological and environmental measures of longitudinal exposure to non-persistent insecticides for individuals and children. Attainment of these outcomes will substantially improve our understanding of neurological disorder incidence, management, and prevention and as a result, has the potential to substantially improve the health of children.

Numerous contemporary and common use pesticides impart their toxicological effects upon biochemical pathways, transmitters, and receptors in insects that are also present in humans. Previous studies with epidemiological, exposure assessment, and toxicological designs and objectives indicate that neurological function of developing humans can be impaired by exposure to non-persistent insecticides among other factors. These studies suggest that the timing of exposure could profoundly influence risk in conjunction with the conventional exposure metrics of magnitude and duration. There is no commonly recognized method for determination of short-term, longitudinal, or chronic exposure of children to non-persistent insecticides. This knowledge gap is in large part the result of insecticide occurrence in multiple environmental media because of numerous application sites and uses, the transient nature of contemporary insecticides due to their chemical properties, and the within-person and between-person variability of specific activities and behaviors that bring people into contact with insecticides. This lack of knowledge is greatest for children.

Potential for Innovative Research

This hypothesis has a high potential for innovative research. Creative approaches on all fronts, including survey design, technology, and data analysis,

are required to overcome the challenges associated with investigation of longitudinal insecticide exposure and potential health effects. For example, typically studies of cumulative effect focus on chemicals with the same mechanism of action. An example is organophosphate and carbamate insecticides that both operate by reducing cholinesterase activity. Pyrethroids act on the nervous system as well, but influence the neural transfer of sodium ions, rather than cholinesterase inhibition. The proposed investigation presents a unique opportunity to examine health effects arising from cumulative exposure to chemicals with differing mechanisms but perhaps affecting the same endpoint, neurodevelopment.

Feasibility

This research involves critical periods that extend for a period of years, with a high degree of uncertainty regarding specific windows, if any, during those critical periods. This research will also require environmental sampling (including in the home). Pilot work and current work underway at EPA and other institutions may allow for reduced amounts of environmental sampling, as a better understanding of the important pathways for insecticide exposure is gained. Properly designed questionnaires may serve as a surrogate for some environmental sampling. This research will also require periodic sampling of blood and/or urine during the critical period. Often, the metabolites of the insecticide will be measured as a surrogate for the chemical itself, as many of the insecticides are rapidly metabolized. The difficulty with this is that metabolites measured in blood or urine could result from exposure to the metabolite rather than the environmental chemical of interest. The necessary time interval between biological monitoring is uncertain, but will probably coincide with blood sampling and medical examinations related to other hypotheses in the NCS. Some of the insecticides can be monitored non-specifically (e.g. organophosphates differentiated from pyrethroids), but more specific insecticide metabolites may be measured as well. The collection of urine samples is noninvasive and, although a challenge in the very young, is generally simple to perform. Sensitive and specific assays for these insecticides have been developed and are used routinely by the National Center for Environmental Health, U.S. Centers for Disease Control and Prevention and by other organizations. To assess neurodevelopment, outcome measures will need to be determined in consultation with other Working Groups. Careful consideration of information gained by repeated environmental measurements will need to be weighed against costs and participant burden.

Contact: David MacIntosh
Associate Professor
Department of Environmental Health Science
University of Georgia
(706) 542-5542
email: dmac@uga.edu

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